LAPORAN KASUS

Why Are We Still Debating Hydroxyethyl Starch Solutions? High Quality and Volume of Evidence of Harm is Conclusive

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Abstract

Fluid resuscitation is indicated to prevent shock and to restore circulatory volume in cases of sepsis and severe blood loss caused by trauma, burns or surgery. Management of Severe Sepsis and Septic Shock" recommend fluid ss first-line therapy for resuscitation of patients with sepsis and septic shock however, synthetic colloids, like HES, are strongly rejected due to safety concerns.Multicentre randomised studies concluded the detrimental effect of HES on organ function, in particular renal function in severe sepsis.Trials demonstrated that HES was associated with increased risk of acute kidney injury (AKI) in patients with sepsis and these findings were later corroborated by further large studies, such as VISEP, CHEST and 6S. These studies have not reported any differences between HES solutions and have concluded that both 'old' and 'new' HES preparations are associated with an increased risk of kidney injury and mortality.In 2013, following publication of CHEST, VISEP and 6S, which demonstrated increased mortality and AKI/RRT in patients treated with HES, the FDA included details of these adverse events in a black box warning and recommended against the use of HES in critically ill patients. That same year, the EMA pharmaco vigilance risk assessment committee (PRAC) suspended marketing authorisation for all HES products.Given the safety concerns with HES and the current guidance from the FDA and EMA, it is imperative that all physicians are aware of the bans, limitations and risks of using HES. This narrative review aims to discuss the evidence on use of HES in critically ill patients, with a focus on safety data and adverse effects such as acute kidney failure and increased risk of mortality

Key Words: Acute kidney failure, colloids, fluids, sepsis, shock

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Introduction

Intravenous (IV) fluid therapy is an integral component of treatment for critically ill patients in intensive care or the operating room. Fluid resuscitation is indicated to prevent shock and to restore circulatory volume in cases of sepsis and severe blood loss caused by trauma, burns or surgery. However, a central issue is the choice of fluid. Crystalloids and colloids are the most commonly used solutions. Crystalloids, including non-balanced (i.e., normal saline) and balanced (i.e., Ringer's lactate, Ringer's acetate) fluids, are aqueous solutions of mineral salts and other water-soluble molecules that can diffuse across cell membranes. The most commonly used crystalloid solution is normal saline, which is a 0.9% sodium chloride solution. Colloids consist of large molecules that do not easily diffuse across cell membranes, and thus remain in the intravascular space for longer. Due to the oncotic pressure exerted by colloid solutions, they have been regarded as more efficient volume expanders than are crystalloids. Recently, however, it has been established that the volume-sparing effect of colloids is lower than previously assumed (crystalloid to colloid ratios between 1 and 1.45).[1] Colloid fluids include natural colloids such as albumin, and synthetic colloids such as hydroxyethyl starch (HES), dextran and gelatin. Treatment guidelines, such as the "Surviving Sepsis Campaign International Guidelines for Management of Severe Sepsis and Septic Shock" recommend crystalloids as first-line therapy for resuscitation of patients with sepsis and septic shock. Additional use of albumin is recommended in the treatment of hypovolemia, and when patients require substantial amounts of crystalloids, as this can lead to fluid overload; however, synthetic colloids, like HES, are strongly rejected due to safety concerns.[2]

Hydroxyethyl starch is an artificial colloid that has been used for fluid therapy for over half a century; however, its use has been heavily criticised.[3–11] HES was first approved for commercialization in the early 1970s, but this was based upon data from small (total of 315 patients) and uncontrolled studies with short observation periods (< 24h), rather than efficacy and safety data from phase I, II, and III clinical trials.[1,10] Subsequent approvals of modified HES products, with lower molecular weights and which are claimed to have fewer adverse effects, have followed (see Table 1 for a brief timeline of HES).[12]

Large RCTs with sufficient numbers of patients in an ICU setting, including the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study [13], Crystalloid versus Hydroxyethyl Starch Trials (CHEST) [14], and the Scandinavian Starch for Severe Sepsis/Septic Shock (6S)[15] have demonstrated the adverse effects of HES, including increased rates of acute kidney injury (AKI), renal replacement therapy (RRT) and mortality. Following these findings, all HES products, irrespective of molecular weight, are prohibited by US and EU regulatory bodies as fluid therapy in patients who are critically ill and those with severe sepsis/septic shock, and their use is also heavily restricted in trauma and surgical patients: no prophylactic use; use for 24 hours only; limited dosing; not to be used in patients with coagulation abnormalities; 90-day observation period.[16–18] Yet publications in favour of HES continue to emerge [19–22], with studies purporting to show safety in surgical settings and during initial hemodynamic stabilization, despite serious methodological flaws and insufficient evidence.[7, 23–25]

Given the safety concerns with HES and the current guidance from the FDA and EMA, it is imperative that all physicians are aware of the bans, limitations and risks of using HES. This narrative review aims to discuss the evidence on use of HES in critically ill patients, with a focus on safety data and adverse effects such as acute kidney failure and increased risk of mortality.

The harms of HES: Clinical evidence to date

In early studies, the safety of HES was not adequately assessed. Nonetheless, even earlier studies reported that HES products interfered with coagulation, leading to increased bleeding.[26–28] Soon after, other adverse effects, such as impaired renal function and pruritus, and evidence of tissue storage started to emerge.[29–34] However, because the early studies were small and underpowered,[35] the true scale of the adverse effects associated with HES solutions was not clearly evidenced until the early 2000s. In 2001, a randomised controlled trial (RCT) by Schortgen et al. was

Table 1 A brief timeline of HES

Year	Event
1972	First HES solution approved by FDA (Hespan® 6% HES 600/0.7)
1975	Evidence of HES interference with coagulation [28]
1982	Early evidence of pruritus after HES administration [33]
1993/1996	First reports of renal failure [30, 31]
2001	RCT demonstrating increased risk of AKI in patients with sepsis treated with HES [36]
2002	An FDA hearing sought to determine the effects of Hespan® and Hextend® on coagulation and blood loss. As per a presentation given by Dr Gan the regulators issued a black box warning for Hespan® but not Hextend® [91]
2007	Approval of 6% HES 130/0.4 (Voluven) by the FDA [92]
2008	RCT reporting higher mortality, AKI and RRT in patients with severe sepsis resuscitated with HES [13]
2012	Two RCTs finding increased need of RRT in ICU patients [14], and RRT and mortality in patients with severe sepsis [15] treated with HES
2013	FDA issues a box warning for all HES products about the risk of renal injury and mortality in critically ill patients [17]. An additional warning about excessive bleeding was initially inserted, but later removed [17] EMA recommends not to use HES in patients with sepsis, burn injuries or critically ill, and requested post-authorisation commitment to additional studies in patients with trauma and in elective surgery [93]
2013-2015	Numerous systematic meta-analyses and reviews published associating HES use to renal failure and mortality in various clinical settings [37-43]
2017	Letter to the EMA [74] and petition to the FDA [73] to ban HES products

HES: Hydroxyethyl starch; FDA: US Food and Drug Administration; RCT: randomised clinical trial; AKI: acute kidney injury; RRT: renal replacement therapy; ICU: intensive care unit, EMA: European Medicines Agency

one of the first adequately controlled studies to demonstrate the adverse effects of HES.[36] This multicentre, randomised study was designed to assess the effect of HES on organ function, in particular renal function in severe sepsis.30,31 The trial demonstrated that HES was associated with increased risk of acute kidney injury (AKI) in patients with sepsis (odds ratio [OD] 2.57; 95% confidence interval [CI] 1.13–5.83); these findings were later corroborated by further large studies, such as VISEP, CHEST and 6S.[13-15] The results from these studies also demonstrated that use of HES in severe sepsis and intensive care patients is associated with higher rates of acute kidney injury and renal replacement therapy, and increased risk of mortality.

Data from these studies is corroborated by systematic reviews and meta-analyses.[37–43] For instance, in 2013 Mutter et al. published a revised Cochrane review that included 42 RCTs with a total of 11,399 patients, including 8 studies in 3,899 patients with sepsis or burns and 11 studies in 5,911 non-septic patients (surgical and trauma). To date this is the largest meta-analysis of the safety of HES products as compared with other fluid therapies. The primary outcomes studied were the need for RRT, and AKI based on RIFLE criteria for Risk, Injury or Failure (as separate outcomes); however; where these data could not be obtained, "author defined" kidney failure was analysed as the outcome. Most HES products studied were 6% solutions of 130/0.4, 200/0.5, 200/0.6 or 450/0.7, compared with various intravenous fluids, including crystalloids, albumin, gelatin, and blood or fresh frozen plasma. The meta-analysis reported an overall significant increase in the need for RRT in all patients treated with HES compared with other fluids (19 studies, 9,857 patients; risk ratio [RR] 1.31, 95% CI 1.16–1.49), as well as increased risk of AKI based on RIFLE-F (failure) (15 studies, 8,402 patients; RR 1.14, 95% CI 1.01–1.30) and author-defined kidney failure (15 studies, 1,361 patients; RR 1.59, 95% CI 1.26–2.00). No significant differences in the risk for RRT or RIFLE-F were observed between septic and non-

Table 2 Summary of large RCTs demonstrating adverse effects of HES

RCT	Setting	n° patients	Fluid		Outcome			
			Intervention	Control	28-day mortality	90-day mortality	AKI	RRT
VISEP [13]	Severe sepsis	600	10% HES 200/0.5	Ringer's lactate	26.7% vs. 24.1%, p = 0.48	41% vs. 33.9%, p = 0.09	34.9% vs. 22.8%, p = 0.002	31% vs. 18.8%, p = 0.001
CHEST [14]	ICU	7000	6% HES 130/0.4	0.9% saline	13.8% vs. 13.1%, p = 0.40	18% vs. 17%, p = 0.26	10.4% vs. 9.2%, p = 0.12	7% vs. 5.8%, p = 0.04
6S [15]	Severe sepsis	804	6% HES 130/0.4	Ringer's acetate	39% vs. 36%, p = 0.43	51% vs. 43%, p = 0.03	-	87% vs. 65%, p = 0.04

RCT: Randomised Clinical Trial; ICU: intensive care unit; AKI: acute kidney injury; RRT: renal replacement therapy

septic patient groups. Furthermore, the significant increase in the need for RRT was observed for both high-molecular weight (9 studies, 1,183 patients; RR 1.56, 95% CI 1.15–2.11) and low-molecular weight (10 studies, 8,353 patients; RR 1.26, 95% CI 1.09–1.45) HES compared with other fluids, as well as for both high-volume (≥2 L) (10 studies, 2,220 patients; RR 1.43, 95% CI 1.20–1.71) and low-volume (<2 L) (7 studies, 7,296 patients; RR 1.22, 95% CI 1.02–1.46) HES administration.

Long-term efforts to produce safer HES solutions by lowering its molecular weight and/or degree of molar substitution failed. Compared with early HES solutions (e.g., HES 450/0.7 [670/0.75], 200/0.62, 200/0.5, 70/0.5), newer HES solutions, such as HES 130/0.4, have a low molecular weight and degree of molar substitution and are often referred to as 'new' or 'modern' in a non-scientific attempt to differentiate them from the older formulations. However, while 'new' HES solutions are claimed to demonstrate improved safety,[12] much of the clinical evidence used to support an improved safety profile for these solutions came from studies which have now been retracted due to fraudulent and/or unethical research. Since then, numerous meta-analysis and reviews have included pair-wise comparisons of 'new' (i.e., low-molecular weight and substitution) HES and 'old' (i.e., high-molecular weight and degree of substitution) HES (see for instance the results from Mutter et al. 2013 detailed above). These studies have not reported any differences between

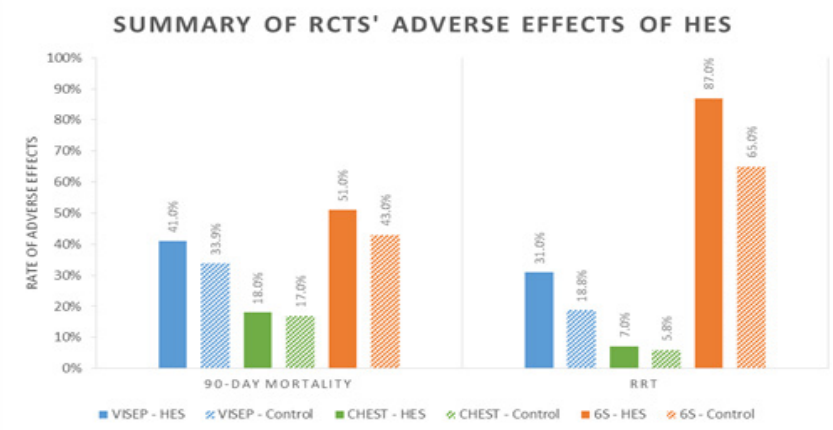

Figure 1 Summary of large RCTs reported adverse effects of HES

Table 3.Summary of recommendations on HES from regulatory and scientific bodies

	Indications	Contraindications	Restrictions/Monitoring
US Food and Drug Administration	- Hypovolaemia	-Renal failure - Critically ill - Sepsis - Intensive care -Pre-existing renal function - Severe liver disease - Pre-existing bleeding or coagulation disorders - Patients on dialysis - Congestive cardiac failure - Hypersensitivity - Clinical conditions with volume overload	- Discontinue at first sign of renal injury - Avoid fluid overload - Adjust dosage with cardiac or renal dysfunction - Monitor fluid balance - Monitor serum electrolytes - Monitor renal and hepatic function - Monitor renal function for at least 90 days - Monitor coagulation parameters - Monitor liver function
European Medicines Agency	- Crystalloids as first choice in hypovolaemia - HES indicated to treat hypovolaemia caused by acute blood loss only when crystalloids are insufficient	- Sepsis - Burns - Critically ill - Renal failure - Renal impairment or renal replacement therapy - Hyperhydration - Lung oedema - Intracranial bleeding - Hypersensitivity - Congestive cardiac failure - Severely impaired of liver function - Hyperkalaemia - Severe hypernatremia or hyperchloraemia - Clinical conditions with volume overload - Severe coagulopathy - Organ transplant patients - Open heart surgery patients - Trauma and surgery: consider other options	- Limited to first 24 hours - Discontinue at first sign of renal injury or coagulopathy - HES solutions should be at the lowest effective dose for the shortest period of time (max daily dose 30 mL/kg) - Infusion to be stopped as soon as appropriate haemodynamic goals are achieved (must not exceed max daily dose) - Monitor fluid balance - Monitor serum electrolytes - Monitor renal and hepatic function - Monitor renal function for at least 90 days - Monitor coagulation parameters - Continuous haemodynamic monitoring
Surviving Sepsis Campaign	- Crystalloid as first fluid of choice in patients with sepsis and septic shock - Albumin as an adjuvant when patients require substantial amounts of crystalloids	- HES not recommended in patients with sepsis and septic shock	

HES solutions and have concluded that both 'old' and 'new' HES preparations are associated with an increased risk of kidney injury and mortality.[35, 37, 39, 44–46] Furthermore, evidence against both 'old' and 'new' preparations of HES strengthened after the retraction of numerous fraudulent studies by Boldt and co-workers.[11] These, when analysed together with legitimate studies, strongly contributed to masking the true adverse effects of HES for many years.[40] Zarychanski et al. (2013) examined the effect of studies by Boldt on AKI and mortality outcomes. Thirty-five trials (10,880 patients) included in the mortality data analysis revealed a RR for death among HES-

treated patients of 1.07 (95% CI 1.00–1.14). However, this analysis included seven trials by Boldt which, when analysed separately, did not reveal a significant association between HES and mortality (590 patients; RR 0.91, 95% CI 0.74–1.12). When these seven fraudulent studies by Boldt were excluded, the analysis demonstrated increased mortality (10,290 patients; RR 1.09, 95% CI 1.02–1.17), renal failure (8,725 patients; RR 1.27, 95% CI 1.09–1.47) and use of RRT (9,258 patients; RR 1.32, 95% CI 1.15–1.50) associated with HES administration. Furthermore, these seven trials by Boldt were the source of high statistical heterogeneity between trials; once the trials were removed from the meta-analysis, the strength of evidence of harm increased and between-trials heterogeneity decreased.

Key clinical trials: Analysis and controversies

In 2008, the first of three large RCTs demonstrating adverse effects of HES compared with crystalloids was published (see Table 2 and Figure 1). The VISEP [13] study investigated fluid resuscitation with HES 200/0.5 versus Ringer's lactate in patients with severe sepsis. The results demonstrated a significantly higher 90-day mortality rate, and a greater incidence of acute kidney injury (AKI) and need for renal replacement therapy (RRT) in patients treated with HES 200/0.5 compared with Ringer's lactate. Similarly, the CHEST and 6S trials investigated the effects of fluid resuscitation in critically ill patients treated with HES 130/0.4 compared with crystalloids.[14,15] Both RCTs reported an increase in patients requiring RRT in the HES-treated group versus crystalloids [14, 15]; additionally, 6S demonstrated an increase in 90-day mortality (see Table 2 for details).[15]

Following these RCTs, several comprehensive systematic reviews endorsed and strengthened the evidence that HES solutions increase the risk of renal failure and mortality.[37–43] Patel et al. (2013) demonstrated that use of low-molecular weight HES (6% HES 130/0.4 and 130/0.42), when compared with crystalloids, is associated with increased 90-day mortality (6 studies, 3,033 patients; RR 1.13, 95% CI 1.02–1.25) and need for RRT (RR 1.41, 95% CI 1.08–1.84) in patients with sepsis.[42] Additionally, Haase et al. reported increased risk of RRT in patients with sepsis treated with HES 130/0.38-0.45 compared with other fluids (5 studies, 1,311 patients; RR 1.36, 95% CI 1.08–1.72).[41] Similarly, Rochwerg et al (2015) and Serpa Neto et al (2014) extended these findings to both high- and low-molecular weight HES solutions.[39, 43]

Rochwerg et al. performed a network meta-analysis (NMA) to study the association of different resuscitation fluids (crystalloids, albumin, gelatin, low-molecular weight HES and high-molecular weight HES) with RRT in patients with sepsis. Patients treated with HES showed an increased risk for RRT versus crystalloids (NMA OD 1.39; 95% credibility interval [CrI] 1.17–1.66].

Similarly, Serpa Neto et al. analysed 10 randomised trials of HES solutions versus other fluids in 4,624 patients with sepsis and reported an increased rate of AKI (RR 1.24, 95% CI 1.13–1.36), need for RRT (RR 1.36, 95% CI 1.17–1.57) and 90-day mortality (RR 1.14, 95% CI 1.04–1.26) in patients resuscitated with HES, independent of the type of HES (10% HES 200/0.5 vs. 6% HES 130/0.4). Moreover, other reviews have reported increased mortality, renal injury and RRT in both septic and non-septic patients (acutely ill, trauma, burns, surgery, hypovolemia) treated with HES, irrespective of its molecular weight.[37,38, 40]

Gattas et al. performed a meta-analysis of fluid resuscitation with 6% HES 130/0.4 and 130/0.42 in acutely ill patients, not restricted to sepsis, and found an increased risk of RRT (11 studies, 8,496 patients; RR 1.25, 95% CI 1.08–1.44) and mortality (25 studies, 9,411 patients; RR 1.08, 95% CI 1.00–1.17) in patients treated with 6% HES versus other resuscitation fluids. Based on the cumulative evidence to date, it is clearly established that HES is associated with detrimental adverse effects (e.g., AKI, RRT and mortality) and its use cannot be recommended in intensive care and critically ill patients. This recommendation is supported by regulatory bodies, such as the EMA and FDA, and in treatment guidelines such as those from The Surviving Sepsis Campaign.

Nevertheless, a few RCTs claiming the safety of HES exist; however, serious limitations are evident upon close examination of their study designs.[47,48] The CRYSTalloids Morbidity

Associated with severe Sepsis (CRYSTMAS) trial compared 6% HES 130/0.4 and 0.9% saline in the treatment of 196 patients with severe sepsis.[47] The study was designed to fulfil post-marketing requirements requested by the FDA and initially reported no differences in adverse effects between resuscitation fluids (28-day mortality: 31% vs. 29%, p = 0.37; 90-day mortality: 40% vs. 34%, p = 0.33; AKI: 24.5% vs. 20%, p = 0.454; for HES and 0.9% saline, respectively).

However, the trial was limited by its small sample size, which precluded it from accurately assessing renal failure or RRT, and received criticism for selective reporting, hiding adverse effects of HES.[49, 50] Similarly, the Fluids in Resuscitation of Severe Trauma (FIRST) trial compared 6% HES 130/0.4 with 0.9% saline in the resuscitation of 115 patients with blunt or penetrating trauma.[48] This trial reported no differences in renal injury in blunt trauma (20% vs. 14% for HES and saline respectively, p = ns) and reduced incidence of renal injury in penetrating trauma patients treated with HES (0% vs. 16%, p = 0.018).

However, the study not only downplayed the increased use of blood or blood products in blunt trauma patients treated with HES (mean transfusion of packed red blood cell volumes: 2,943 (1,628) vs. 1,473 (1,071) mL for HES and saline, respectively, p = 0.005), but also was underpowered to assess renal failure, failed to report key data, did not follow CONSORT standards for reporting of endpoints, and employed study groups that were not well matched at baseline.[51,52]

Both CRYSTMAS and FIRST lacked the statistical power required to accurately evaluate differences in renal function, and data were omitted or incompletely reported.[50] The Therapy in the Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) trial analysed the use of colloids (gelatins, dextrans, HES, or 4% or 20% albumin) and crystalloids (isotonic or hypertonic saline or Ringer's lactate solution) for fluid resuscitation in 2,857 critically ill patients.[53] There were no significant differences between groups in 28-day mortality (RR 0.96, 95% CI 0.88–1.04), but 90-day mortality was higher in patients receiving crystalloids compared with colloids (RR 0.92, 95% CI 0.86–0.99). Unfortunately, this study suffered from severe methodological flaws, such as lack of allocation concealment and blinding, heterogeneity of fluids in the study groups, lack of stratification within the two groups of fluids, and main results based on a secondary endpoint with a CI approaching 1.0.[54] As recently emphasized, in order to accurately assess the effects of HES, RCTs need adequate sample size (> 500 patients), control of fluids, and length of follow-up (90-day).[10,55]

Regardless, pro-HES advocates argue that VISEP, CHEST and 6S assessed HES in critically ill patients and that their findings cannot be extrapolated to the operating room.[7] Other arguments include that the adverse effects of HES were due to incorrect administration or infusion of HES, e.g., study drug administration in the maintenance phase, and incorrect follow-up of patients, e.g., after the initial stabilisation phase.[5,23,25,56]

While there is consensus that no evidence exists to support the use of HES in intensive care and/or after initial stabilisation,[7, 57] the benefits and use of HES in the initial resuscitation phase during surgery have been defended, despite a lack of studies and data showing otherwise.[7,56,57] Irwin and Gan [7] advocate that HES should only be used in the operating room for initial hemodynamic resuscitation within < 6 hours from the onset of shock, and should exclude patients with pre-existing renal failure and/or AKI.

However, the safety of HES in the perioperative setting is far from clear due to the lack of large RCTs, mixed outcomes reported in existing studies, and statements based on non-systematic low-quality reviews.[6, 8, 58–60] Crucially, a meta-analysis of 18 RCTs of HES compared with albumin in 970 patients undergoing cardiopulmonary bypass surgery reported significant increases in the following outcomes in patients treated with HES: postoperative blood loss (33.3% increase of a pooled SD, 95% CI 18.2%–48.3%), reoperation for bleeding (RR 2.24, 95% CI 1.14–4.40), and transfusions of red blood cells (28.4% increase of a pooled SD, 95% CI 12.2%–44.6%), fresh-frozen plasma (30.6% increase, 95% CI 8.0%–53.1%), and platelets

(29.8% increase, 95% CI 3.4%–56.2%).[45]

Moreover, no significant differences were found in head-to-head comparisons of HES 130/0.4 with 200/0.5. Another meta-analysis of 15 RCTs in 4,409 patients undergoing surgery demonstrated increased need for RRT in patients receiving HES compared with other solutions (pooled RR 1.44, 95% CI 1.04–2,01).[61] A retrospective study published in 2014 investigated the risk of developing acute AKI following inpatient non-cardiac surgery in 29,360 patients receiving HES or non-colloids.[62]

This study reported a significantly higher risk of developing a more serious AKI with HES than with crystalloids (adjusted OR 1.21, 97.5% 1.06–1.38). There was a significant positive association between the total volume of colloid given and risk of developing more serious AKI (adjusted OR 1.44, 97.5% 1.26–1.64). [62] Most recently, Lagny et al. reported increased rates of postoperative AKI in 606 patients undergoing cardiac surgery who were given 6% HES 130/0.4 intraoperatively, compared with crystalloids (adjusted OR 2.26, 95% CI 1.40–3.80).[63]

While other reviews have not identified differences in the incidence of AKI or mortality in surgical settings, they have nevertheless cautioned against the use of HES in surgical patients. This is based upon insufficient evidence for the benefit of HES, as well as the fact that AKI is a postoperative complication leading to many surgical patients requiring critical care. [64, 65] It has been well established that AKI is a generic adverse effect of all HES products, even though the pathomechanisms for renal injury require further elucidation.

HES has been shown to accumulate in tissues for long periods of time; the kidney in particular has demonstrated high tissue concentrations of HES.[29,66] While storage of HES in the skin causes pruritus, renal uptake of HES into the luminal epithelial cells of the proximal tubules may be the cause of its nephrotoxic effects.[29,67,68]

Future of HES: Updates from scientific and regulatory bodies

In 2013, following publication of CHEST, VISEP and 6S, which demonstrated increased mortality and AKI/RRT in patients treated with HES, the FDA included details of these adverse events in a black box warning and recommended against the use of HES in critically ill patients.[17] That same year, the EMA pharmacovigilance risk assessment committee (PRAC) suspended marketing authorisation for all HES products.[69] However, this initial suspension was challenged by the marketing authorisation holders. Following review of the available evidence by a second assessment committee, HES was contraindicated for use in the treatment of critically ill patients and those with sepsis or burn injuries, in patients with renal impairment or RRT, and in severe coagulopathy; however, HES was allowed for treatment of hypovolaemia due to acute bleeding in patients not responding to crystalloids.

In these patients, the use of HES was limited to 24 hours and to the lowest effective dose for the shortest period of time until achievement of haemodynamic goals, with continuous haemodynamic monitoring and extended monitoring of kidney function for 90 days recommended [16]. Additionally, the PRAC requested post-marketing RCTs to assess HES efficacy and safety in perioperative and trauma patients (for a review of key regulatory decisions see [70]). Despite these restrictions on the use of HES in critically ill patients, there has been strong criticism that the recommendations do not go far enough, and that continued use of HES is based upon unpublished/non-peer-reviewed data and a poorly controlled RCT.[71]

As a result, a recent petition to ban the use of HES products was supported by 80 medical experts.[72–74] Furthermore, the Federal Institute for Drugs and Medical Devices (BfArM, Germany) has suspended the marketing authorisation of all HES-containing products from the company Serumwerk Bernburg AG until the end of 2017.[75]

In light of the overwhelming evidence accumulated to date, HES has no place in the management of critically ill patients or those undergoing surgery. A consensus document from the European Society of Intensive Care Medicine (ESICM) does not recommend HES for fluid therapy in patients with severe sepsis or in those who are at risk of AKI. Furthermore, these guidelines recommend not to use colloids in patients with head injuries, and HES in

organ donors.[44] Similar recommendations can be found in the Surviving Sepsis Campaign International guidelines, which recommend that HES should be avoided for fluid resuscitation in sepsis (see Table 3 for a summary of recommendations on HES products).[2]

While the implementation of the Surviving Sepsis Campaign has improved care and clinical outcomes of critically ill patients, and reduced mortality related to sepsis,[76] physicians' awareness remains a challenge in middle- and low-income countries. Additionally, following the EMA and FDA measures against the use of HES, some regulatory bodies, such as the China Food and Drug Administration (CFDA), published a statement but did not explicitly prohibit the use of HES in the ICU and for the treatment of critically ill, septic and burns patients.[77,78]

Although many countries, including China, Japan, Mongolia and Turkey adopted the Surviving Sepsis Campaign guidelines several years ago, multicentre studies and surveys have revealed a general lack of awareness and knowledge of these among their physicians and other healthcare professionals.[79–82] In 2011, a prospective cohort study including 1,285 patients with severe sepsis admitted in 16 Asian intensive care units found that compliance with the Surviving Sepsis Campaign was poor in most Asian hospitals.[83] A recent multicentre study of shock patients admitted to Chinese ICUs reported excessive use of HES, which was associated with increased mortality.[84]

This study emphasizes the importance of awareness and implementation of the Surviving Sepsis Campaign guidelines in ICUs and the need for regulators in these countries to act. A German company (Serumwerk Bernburg) announced profit increases in the wake of the HES ban in Europe; they continued to sell the product in large quantities to non-EU countries irrespective of the established dangers associated with it.[85] Furthermore, even when physicians' knowledge on management of sepsis and septic shock is adequate, a lack of resources in middle- and low-income countries hinders the implementation of the Surviving Sepsis Campaign guidelines.[79] Critical care and intensive care units are under-resourced in low-income countries; [86] therefore, education and awareness of the diagnosis and management of sepsis and septic shock should be adapted to the resources available in middle- and low- income countries.[87]

Finally, recently published results from an international cross-sectional study comparing IV fluid use in ICUs between 2007 and 2014 reported a significant overall decrease in the use of HES between during this period (35.4% vs. 7.4%, respectively).[88] Even though there was regional variability, this overall observed pattern of decreased HES use offers confidence of a global increasing acknowledgement of the HES harms and its rejection as an IV fluid.

Conclusions

Since HES was first introduced into the market there has been continued denial of recurrent safety issues. Studies supporting the use of HES have been demonstrated to be poorly designed and underpowered, and proponents rely on non-systematic low-quality reviews.[10,55,58–60]. There is now a large body of evidence from well-designed RCTs and systematic reviews indicating that HES, independent of its molecular weight and degree of molar substitution, is associated with numerous adverse events, such as acute kidney failure and increased risk of RRT and mortality.13–15, 37–43Given that there is no indication of a clear benefit of HES over its comparators but that there are numerous safety concerns- and it is not possible to predict which patients will suffer them -the use of HES in critically ill patients should be banned completely. Its use in the operating room should also be avoided, with restricted use in future only if post-authorisation commitments are satisfied with high-quality data. These recommendations and findings are supported by large, high-quality RCTs with low risk of bias and which form the basis of scientific guidelines and regulatory bodies' decisions to advocate the use of safer alternatives, such as crystalloids and albumin (which shows nephrotective potential [89, 90]) where appropriate, instead of HES.

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